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Opinion of the Scientific Committee on Food on Tahitian Noni® juice

(expressed on 4 December 2002)

B-1049 Bruxelles/B-1049 Brussels - Belgium
Telephone: direct line (+32-2) 29 599.10, exchange 299.11.11. Fax: (+32-2) 299.48.91
Telex: COMEU B 21877. Telegraphic address: COMEUR Brussels.

http://europa.eu.int/comm/food/fs/sc/scf/index_en.html

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1. TERMS OF REFERENCE

With reference to the initial assessment carried out by the authorities of Belgium, taking into account the relevant comments/objections presented by Member States and pursuant to Article 11 of Regulation 258/97/EC, the Committee is asked to assess the safety, from the point of view of consumer health, of Tahitian Noni® juice.

2. BACKGROUND

Within the framework of Regulation 258/97/EC on novel foods and novel food ingredients, a request for authorisation to place Tahitian Noni® juice, a fruit juice based on Noni (the common name for *Morinda citrifolia* L.), as a novel food on the market in the Community has been received.

Tahitian Noni® juice is a fruit juice mixture of 89% Noni fruit (*Morinda citrifolia* L.) and 11% common grape and blueberry juice concentrates and natural flavours. The applicant considers that it would be consumed in the form of fruit juice with a suggested level of consumption of 30 mL/day.

Morinda citrifolia has been consumed in Polynesia and South East Asia. Tahitian Noni® juice has been marketed in the USA (since 1 July 1996), in Canada, Japan, Australia, Mexico, Norway and Hong Kong.

This opinion takes into account *(a)* the original information submitted by the applicant, *(b)* the initial assessment carried out by the Belgian Competent Authority, *(c)* comments/objections to the initial assessment report forwarded by the Member States, and *(d)* responses by the applicant to the comments made by the Member States and to questions raised by the Committee.

The rejection by the Belgian Competent Authority has been based on the following reasons:

- A safety factor of 100 was applied to convert the No Observed Adverse Effect Level (NOAEL) of 80 mL/kg body weight/day determined in a 13-week gavage study with rats into an Acceptable Daily Intake (ADI) in man of 0.8 mL/kg body weight/day. Based on body weights from 20 to 80 kg, this corresponds to intakes ranging from 16 mL/day to 64 mL/day per person. These values were considered very low and further toxicological tests at higher doses were requested.

- The information supplied concerning the novel food's probable place in the diet and its level of use was not considered to be satisfactory.

Objections by Member States focused on:

- compositional data, including natural variations,
- compounds of toxicological/pharmacological relevance,
- suggested level of consumption/serving-size,
- internet advertisement with health or pharmacological claims concerning Noni-based foods,
- categorisation as food *vs*. medicinal food or nutritional supplement,
- tests for genotoxic potential (Ames test, micronucleus test),
- details of allergy studies.

3. EVALUATION

The product belongs to class 2, sub-category 2.2 (novel foods derived from sources which have not been genetically modified and which have no history of food use within the Community), as defined in the SCF recommendations concerning the assessment of novel foods (European Commission, 1997). Accordingly, information related to the structured schemes I, II, III, IX, XI, XII, XIII has been submitted. In addition, the applicant also provided data related to scheme X (previous human exposure to the novel food).

3.1 Compositional data

Tahitian Noni® juice is already produced on a commercial scale. A typical compositional profile is given in Annex 1.

A Quality Assurance Policy and Procedure Manual adopted by the applicant to ensure the consistency of products has been submitted. Analytical data on individual batches of Tahitian Noni® juice as well as a summarising table reporting means, minimum and maximum contents of selected constituents have been provided. The samples used for toxicological tests have been analysed and shown to be representative of commercial products.

Members of the family Rubiaceae, such as *Morinda citrifolia* L., are known to contain anthraquinones in the roots. Anthraquinones could be isolated from cell suspension cultures of *Morinda citrifolia* (Leistner, 1975). However, in accordance with formerly published data (Zenk *et al.*, 1975), these constituents could not be identified in Noni fruits. Data from analyses submitted by the applicant paid particular attention to lucidin and rubiadin, because of the genotoxicity of these two anthraquinones. Neither compound was detected in the juice (detection limit determined for rubiadin: 10 µg/kg).

Using the method described by Song *et al.* (1998), none of eight frequently occurring isoflavones (genistin, genistein, daidzin, daidzein, glycitin, glycitein, formonoetin, biochanin A) could be detected in Tahitian Noni® juice.

A typical feature of Noni fruit is the presence of free fatty acids which contribute to its unpleasant flavour (Farine *et al.*, 1996). These compounds are known food volatiles (Jeon, 1994).

3.2 Effect of the production process applied to the novel food

The fruits are harvested by hand. Seeds and skin are separated mechanically from the pureed fruits. After pasteurisation, the puree is packaged in aseptic containers for shipment. The puree is reconstituted and blended with other fruit juice concentrates (grape juice concentrate, blueberry juice concentrate) and natural flavours. The resulting blended juices (89% Noni fruits) are pasteurised (87.7 °C for three seconds) and bottled. This production process is a standard procedure commonly applied in fruit juice manufacture and does not give rise to concern.

3.3 History of the organism used as the source of the novel food and previous human exposure to the novel food or its source

Taxonomically, *Morinda citrifolia* L. belongs to the Rubiaceae family. Common names are "Indian Mulberry", "Noni", and "Nonu". The shrub or small tree occurs from India through Southeast Asia to Eastern Polynesia. It has a long tradition as valuable dye plant, as medicinal plant and as food for the aboriginal populations.

Dye use. Due to the presence of anthraquinone derivatives in roots and bark, these parts of the plant have been used as sources for colouring agents (Thomson, 1971).

Medicinal use. Morinda citrifolia L. has long been employed throughout Polynesia as folk medicine. The use of virtually all parts of the plant (fruit, leaf, bark, root, flower and seed) has been described to treat boils, cuts, abscesses and inflammations of various types, fungal infections, constipation and diarrhoea (Hirazumi, 1997).

Food use. Several ethnobotanical studies from tropical regions refer to raw or cooked *Morinda citrifolia* L. fruit (Noni fruit) as part of the diet of aboriginal populations of Polynesia and Australia (e.g., Brown, 1935; Cheeseman, 1903; Morton, 1992; Sturtevant, 1919). According to some references (Krauss, 1993; Uhe, 1974; Whistler, 1992), the consumption was limited to times of famine due to the rather unpleasant taste and foul odour of the ripe fruits.

Tahitian Noni® juice has been marketed for several years in a number of countries. According to data obtained in the USA for a 4-month period in 2002, an average number of around 300,000 one-litre bottles were sold per month.

3.4 Anticipated consumption/level of use of the novel food

The applicant intends to place the product on the EU market as a whole food (fruit juice). The product would not replace any others. Suggested consumption is 30 mL per day.

According to the applicant, the recommended 30 mL/day serving-size was not based on an anticipated pharmacological effect, an anticipated nutritional effect or toxicological data. The recommendation has been used as standard means of measurement and calculation for marketing purposes. Because of the costs and the unique flavour of the juice, the applicant's

intention has been to market Tahitian Noni® juice as an aperitif-like food. The recommended serving size is intended to correspond to the USA listed nutritional facts label.

According to data obtained in the USA for 2001, an average number of 46,603 people purchased Tahitian Noni® juice per month. 73.7% purchased 4 bottles per month. Assuming that the purchaser is the only consumer, this is equivalent to a daily consumption of 133 mL. The percentages purchasing 8 bottles (equivalent to 267 mL per day), 12 bottles (equivalent to 400 mL per day) and 16 bottles (equivalent to 533 mL per day) per month are 10.4, 4.2 and 2.2%, respectively.

3.5 Nutritional information on the novel food

The composition of Tahitian Noni® juice in terms of macronutrients, vitamins and minerals is comparable to the ranges known for typical fruit juices. The compositional information presented does not indicate any detrimental nutritional effect arising from the consumption of the juice. Although some nutritional benefits are claimed for *Morinda citrifolia* L. products, the data supplied and the information available to the Committee provided no evidence for special nutritional benefits of Tahitian Noni® juice which go beyond those of other fruit juices.

3.6 Microbiological information on the novel food

By applying Good Agricultural Practices (GAP), Good Hygienic Practices (GHP), Good Manufacturing Practices (GMP) and pasteurisation (87.7 °C for three seconds) the product is to be regarded as microbiologically safe.

3.7 Toxicological information on the novel food

3.7.1 Acute toxicity

LD_{50} values higher than 15,000 mg/kg body weight for juice and puree, respectively, from Tahitian Noni® fruit and higher than 5000 mg/kg body weight for Tahitian Noni® concentrate have been determined in acute oral toxicity studies with rats (PSL, 1999a, b and c).

3.7.2 Subacute toxicity

Twenty Sprague-Dawley rats (10 males and 10 females) were given sterile water (controls, group 1) or 1000 mg/kg body weight of an aqueous extract (5.1% total solids) of *Morinda citrifolia* (group 2) for 28 days by gavage. No treatment-related effects on body weight, food consumption, haematological, clinical chemistry and histopathological parameters were observed (Mancebo *et al.*, 2002).

3.7.3 Subchronic toxicity

Male and female Sprague Dawley rats (10 per group) were given sterile water (controls, group 1), 0.4 (group 2), 4 (group 3) or 8 (group 4) mL Tahitian Noni® juice/kg body weight/day for 13 weeks, daily by gavage. Clinical signs were recorded daily, body weight and food consumption were recorded weekly. Ophthalmoscopic examination was performed on all animals before start of treatment and before necropsy and in groups 1 and 4 at the end of treatment. Blood samples for haematology and clinical chemistry were taken from all animals. At termination of the study the animals were killed, examined macroscopically, weights of

selected organs were recorded, and selected tissues were evaluated microscopically. No treatment-related effects were seen in any parameters evaluated. The No Observed Adverse Effect Level (NOAEL) was 8 mL/kg body weight/day (Glerup, 2000).

In an analogous study male and female Sprague Dawley rats (10 per group) were given sterile water (controls; group 1), or non-concentrated (group 2), 2.5 times concentrated (group 3) and 4 times concentrated (group 4) Tahitian Noni® juice for 13 weeks, by gavage at a volume of 20 mL/kg body weight/day. The NOAEL was 20 mL of 4 times concentrated Tahitian Noni® juice/kg/day. This is equivalent to 80 mL Tahitian Noni® juice/kg body weight/day (Glerup, 2001).

Both studies were conducted in accordance with the methods recommended in the OECD Guideline (OECD, 1998).

3.7.4 Genotoxicity

3.7.4.1 V79-HPRT-test

A V79-HPRT (Hypoxanthine-phosphoribosyl-transferase)-test using the V79-cell line derived from Chinese hamster lung fibroblasts was performed. The test was carried out according to the procedure described by Jensen (1984). The test material was obtained by extracting Tahitian Noni® juice with ethyl acetate. After evaporation of the solvent, the residue was dissolved in dimethyl sulfoxide resulting in a solution containing the ethyl acetate-extractable components of Tahitian Noni® juice in 100-fold concentration compared to the original juice. The test was performed with concentrations of the test material ranging from 0.003 to 3 µL/mL culture medium. Genotoxicity of the test compound was not observed, neither in the presence nor in the absence of S9-mix (Westendorf, 2002a).

3.7.4.2 In vivo-in vitro UDS assay in rat hepatocytes

The UDS (Unscheduled DNA Synthesis) test was performed as *in vivo-in vitro* assay according to the procedure described by Mirsalis and Butterworth (1980) and Westendorf (1993). The concentrated ethyl acetate-extract described for the V79-HPRT-test was used as test material. The experiment consisted of 4 groups of 3 male Wistar rats each. Group 1: saline (negative control); group 2: 10 mg N,N-dimethylnitrosamine/kg body weight (positive control for 2 h treatment) and 50 mg/kg body weight 2-acetylaminofluorene (positive control for 12 h treatment), respectively, diluted in physiological saline; group 3: 1000 mg test compound/kg body weight; group 4: 100 mg test compound/kg body weight. The effects observed for the two groups with the test compound were comparable to the negative control. There was no evidence for a genotoxic potential in rats after oral administration of a solution containing ethyl acetate-extractable components of Tahitian Noni® juice in a dose equivalent to 100 g Tahitian Noni® juice/kg body weight (Westendorf, 2002b).

3.7.4.3 Mouse micronucleus test

A Mouse Micronucleus Test was performed in accordance with the OECD guideline (OECD, 1997). The test material was prepared by mixing the residue (14.7% of the original weight) obtained after distillation of Tahitian Noni® juice under vacuum with physiological saline solution. In a preliminary test groups of two male and two female mice were treated with the residue at 1 and 10 g/kg body weight by gavage on two occasions separated by 24 hours. No adverse reactions were observed and 10 g/kg body weight was selected as the dose level for

the subsequent main test, which was performed with a group of male mice. A negative control group was dosed with 0.9% NaCl, and a positive control group was dosed with cyclophosphamide at 20 mg/kg body weight. No adverse reactions to treatment were observed in the mice. No biologically or statistically significant increases in the frequency of micronucleated polychromatic erythrocytes were seen in mice treated with the residue of Tahitian Noni® juice but also no signs of systemic toxicity were seen (Edwards, 2002).

The Committee noted that the genotoxicity tests were carried out with different test materials obtained from Tahitian Noni® juice. Moreover, in the *in vivo* assay no cytotoxic effects were observed; therefore, no evidence that the test substances or their metabolites reached the target cells was provided.

3.7.5 Allergenicity

Two test groups of guinea pigs (6 per group), one negative control group (6 animals) and one positive control group (3 animals) were induced with four subcutaneous injections of Tahitian Noni® juice one week apart. After a two-week period the animals were challenged by gavage (Tahitian Noni® juice) and by intravenous injection (positive control: ovalbumin), respectively. All visible signs of ill health and any changes in behaviour were recorded during daily inspections. Under these experimental conditions, it was concluded that there was no indication that Tahitian Noni® juice stimulated an acute allergic response in guinea pigs (Kaaber, 2000).

In an additional experiment, three groups of guinea pigs (10 per group) were injected intraperitoneally with 6 mL of Tahitian Noni® juice, puree and concentrate, respectively (10% w/w in distilled water) three days per week for two successive weeks. After the last injection, the animals were allowed to rest for thirty-two days. Thereafter, the guinea pigs were challenged by gavage with dose levels of 0.86 (100% puree or Tahitian Noni® juice) and 0.014 (10% w/w of concentrate in distilled water) mL/kg body weight. During administration and the 60-75 minutes thereafter, the animals were observed for reactions. No antigenic response was observed. Three control groups (5 animals per group) were maintained under identical environmental conditions and treated with the test articles at challenge only. No positive control was included in the experiment. (PSL, 2000).

3.8 Oher reported biological effects

Intraperitoneal injection of an ethanol-insoluble material (Noni-precipitate), obtained from the juice of the *Morinda citrifolia* fruits, has been shown to prolong the lifespan of mice implanted with Lewis lung carcinoma. It was suggested by the authors that the suppression of tumour growth was due to enhancement of the host immune system by a partially identified polysaccharide (Hirazumi *et al.*, 1994 and 1996; Hirazumi and Furusawa, 1999). Glycosides (e.g. 2,6-di-*O*-(β-D-glucopyranosyl)-1-*O*-octanoyl-β-D-glucopyranose) isolated from the fruit have been reported to suppress UVB-induced AP-1 activity associated with cell transformations in mouse epidermal cell cultures (Liu *et al.*, 2001; Sang *et al.*, 2002; Wang *et al.*, 1999). The health significance of these observations is unclear.

3.9 Post-market survey data

There was no active survey done after marketing. According to Morinda Inc.'s sales records, 1,216,060 one-litre bottles of Tahitian Noni® juice were sold in the USA from April through July of 2002. In this time period the company received 29 medical-related customer

complaints (13 apparently related to allergic reactions, 11 cases of possible gastrointestinal stress, and 5 miscellaneous issues).

4. DISCUSSION

The Committee was aware of the difficulties in defining the role of Tahitian Noni® juice in the human diet: (a) an intake recommendation of only 30 mL/day is not common for fruit juices, (b) there are general advertisements for pharmacological benefits of *Morinda citrifolia* L., e.g. via Internet, and (c) the applicant has recently filed a patent for a dietary supplement to reduce cellular damage within the human body. The dietary supplement includes reconstituted *Morinda citrifolia* juice from puree of French Polynesian origin and is claimed to scavenge lipid hydroperoxides and superoxide anion free radicals within the body (Morinda, Inc., 2002).

The Committee considered that it was not appropriate to apply a safety factor of 100 to a NOAEL determined in feeding studies with a whole food to derive an ADI.

Tahitian Noni® juice given daily to rats for 13 weeks at oral doses up to an equivalent of 80 mL/kg body weight caused no signs of toxicity. This indicates there is a considerable margin between the highest dose administered to rats, which was without any effects, and the manufacturer's recommended daily serving size of 30 mL (equivalent to around 0.5 mL/kg body weight for a 60 kg adult). For higher consumers (say up to 600 mL/day, equivalent to 10 mL/kg body weight) the margin is smaller but entirely compatible with margins of exposure for other whole foods.

The Committee had asked the applicant to assess the genotoxic potential of Tahitian Noni® juice by performing a test for induction of gene mutations in mammalian cells (preferably the mouse lymphoma *tk* assay) and a test for chromosomal aberrations in mammalian cells. The data sets submitted differ from those requested. The Committee noted some limitations of the *in vivo* assays; however, the Committee considers the overall results as an indication of lack of genotoxic potential for the materials tested.

The Committee noted the current limitations to assess and predict the potential allergenicity of a complex food, such as Tahitian Noni® juice and was aware of the difficulties to use data from animal models for prediction of allergenicity in humans.

5. CONCLUSIONS

The Committee evaluated the safety aspects of Tahitian Noni® juice as a novel food. The Committee concluded that there were no indications of adverse effects from laboratory animal studies on subacute and subchronic toxicity, genotoxicity and allergenicity. The Committee noted that Tahitian Noni® juice has been marketed for several years in a number of countries. While there have been no formal tolerance trials or systematic post-launch monitoring, few untoward reactions have been reported. Against this background the Committee considers Tahitian Noni® juice, at the observed levels of intake, as acceptable.

The data supplied and the information available to the Committee provided no evidence for special health benefits of Tahitian Noni® juice which go beyond those of other fruit juices.

Therefore, this conclusion does not constitute an endorsement of respective benefits claimed for *Morinda citrifolia* L. products.

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Annex 1. Compositional Profile of Tahitian Noni® juice

	Content	Unit
Proximate		
Moisture	89-90	g/100 g
Protein	0.2-0.5	g/100 g
Ash	0.2-0.3	g/100 g
Total fat	0.1-0.2	g/100 g
Total carbohydrate	9.0-11.0	g/100 g
Total dietary fiber	0.5-1.0	g/100 g
Fructose	3.0-4.0	g/100 g
Glucose	3.0-4.0	g/100 g
Sucrose	<0.1	g/100 g
Energy	163-197	kJ/100g
Specific gravity	1.015	g/mL
pH	3.4-3.6	
Vitamins		
Vitamin C	3-25	mg/100 g
Vitamin B_1	0.003-0.01	mg/100 g
Vitamin B_2	0.003-0.01	mg/100 g
Vitamin B_6	0.04-0.13	mg/100 g
Vitamin B_{12}	0.1-0.3	mcg/100 g
Folic acid	7.0-25.0	mcg/100 g
Biotin	1.5-5.0	mcg/100 g
Niacin	0.1-0.5	mg/100 g
Pantothenic acid	0.15-0.5	mg/100 g
Vitamin E	0.25-1.0	IU/100 g
Carotene (as vitamin A activity)		
Total beta carotene	18-22	IU/100 g
Total carotene	18-22	IU/100 g
Alpha carotene	6.0-7.0	IU/100 g
All-*trans* beta carotene	6.0-7.0	IU/100 g
Cis-beta carotene	6.0-7.0	IU/100 g
Minerals		
Calcium	20-25	mg/100 g
Iron	0.1-0.3	mg/100 g
Phosphorus	2.0-7.0	mg/100 g
Magnesium	3.0-12	mg/100 g
Molybdenum	0.3-1.0	mg/100 g
Sodium	15.0-40.0	mg/100 g
Potassium	30.0-150	mg/100 g
Salt (as sodium chloride)	0.09-0.12	%

	Content	Unit
Amino acids		
Aspartic acid	30-77	mg/100 g
Threonine	8-11	mg/100 g
Serine	9-12	mg/100 g
Glutamic acid	25-44	mg/100 g
Proline	24-33	mg/100 g
Glycine	10-22	mg/100 g
Alanine	17-33	mg/100 g
Cystine	7-11	mg/100 g
Valine	10-22	mg/100 g
Methionine	1-4	mg/100 g
Isoleucine	7-11	mg/100 g
Leucine	10-22	mg/100 g
Tyrosine	6-11	mg/100 g
Phenylalanine	5-8	mg/100 g
Histidine	4-6	mg/100 g
Lysine	7-11	mg/100 g
Arginine	30-44	mg/100 g
Tryptophan	1-3	mg/100 g